INVENTOR SEARCH

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L4 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:195003 HCAPLUS Full-text
DOCUMENT NUMBER: 140:385609
TITLE: Punaglandins, chlorinated prostaglandins, function as potent michael receptors to inhibit ubiquitin isopeptidase activity
AUTHOR(S): Verbitski, Sheryl M.; Mullally, James E.; Fitzpatrick, Frank A.; Ireland, Chris M.
CORPORATE SOURCE: Department of Medicinal Chemistry, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Journal of Medicinal Chemistry (2004), 47(8), 2062-2070
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclopentenone prostaglandins exhibit unique antineoplastic activity and are potent growth inhibitors in a variety of cultured cells. Recently the dienone prostaglandin, Δ12-PGJ2, was shown to preferentially inhibit ubiquitin isopeptidase activity of the proteasome pathway. It is theorized that isopeptidase inhibition and general cytotoxicity of prostaglandins depend on olefin-ketone conjugation, electrophilic accessibility, and the nucleophilic reactivity of the endocyclic β-carbon. Δ12-PGJ2, which contains a cross-conjugated α,β-unsatd. ketone, was a potent inhibitor of isopeptidase activity, whereas PGA1 and PGA2 with simple α,β-unsatd. pentenones were significantly less potent and PGB1 with a sterically hindered α,β-unsatd. ketone was inactive. To further investigate the proposed mechanism, punaglandins, which are highly functional cyclopentadienone and cyclopentenone prostaglandins chlorinated at the endocyclic α-carbon position, were isolated from the soft coral Telesto riisei. They were then assayed for inhibition of ubiquitin isopeptidase activity and antineoplastic effects. The punaglandins were shown to inhibit isopeptidase activity and exhibit antiproliferative effects more potently than A and J series prostaglandins. Also, the cross-conjugated dienone punaglandin was more potent than the simple enone punaglandin. The ubiquitin-proteasome pathway is a vital component of cellular metabolism and may be a suitable target for antineoplastic agents. These newly characterized proteasome inhibitors may represent a new chemical class of cancer therapeutics.

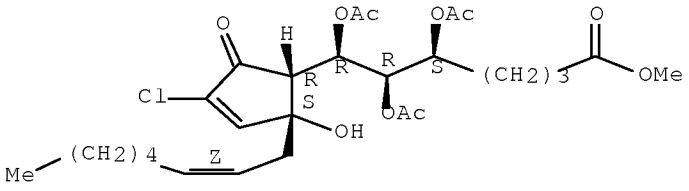
IT 86480-67-3, Ubiquitin isopeptidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(punaglandins function as potent michael receptors To inhibit ubiquitin isopeptidase activity)
RN 86480-67-3 HCAPLUS
CN Hydrolase, ubiquitin thiolester (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 96055-64-0P, Punaglandin 2 96055-65-1P, Punaglandin 3
96055-66-2P, Punaglandin 4 96055-68-4P
160791-07-1P, Punaglandin 6
RL: PAC (Pharmacological activity); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(punaglandins function as potent michael receptors To inhibit ubiquitin isopeptidase activity)
RN 96055-64-0 HCAPLUS
CN Prosta-10,14-dien-1-oic acid, 5,6,7-tris(acetyloxy)-10-chloro-12-hydroxy-9-

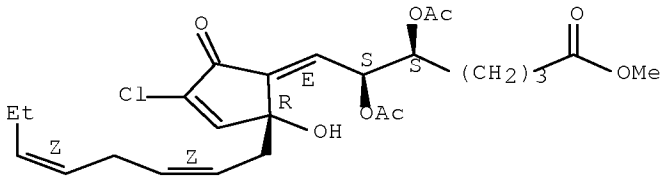
oxo-, methyl ester, (5S,6R,7R,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



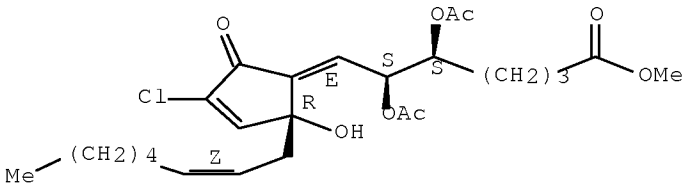
RN 96055-65-1 HCAPLUS
CN Prosta-7,10,14,17-tetraen-1-oic acid, 5,6-bis(acetyloxy)-10-chloro-12-hydroxy-9-oxo-, methyl ester, (5S,6S,7E,14Z,17Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



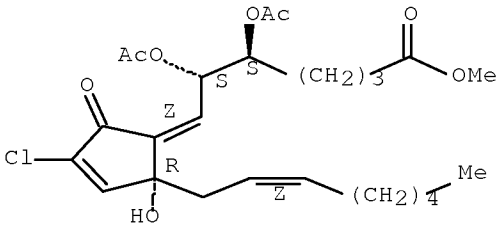
RN 96055-66-2 HCAPLUS
CN Prosta-7,10,14-trien-1-oic acid, 5,6-bis(acetyloxy)-10-chloro-12-hydroxy-9-oxo-, methyl ester, (5S,6S,7E,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



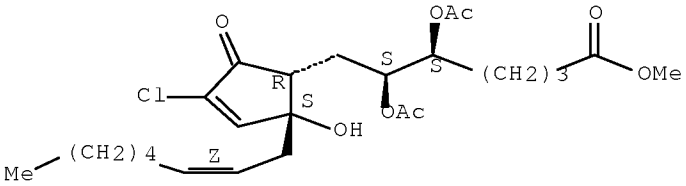
RN 96055-68-4 HCAPLUS
CN Prosta-7,10,14-trien-1-oic acid, 5,6-bis(acetyloxy)-10-chloro-12-hydroxy-9-oxo-, methyl ester, (5S,6S,7Z,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 160791-07-1 HCAPLUS
CN Prosta-10,14-dien-1-oic acid, 5,6-bis(acetyloxy)-10-chloro-12-hydroxy-9-oxo-, methyl ester, (5S,6S,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:80455 HCAPLUS Full-text
DOCUMENT NUMBER: 140:139470
TITLE: α,β-unsaturated ketone as inhibitors of ubiquitin isopeptidases that induce p53-independent cell death and their therapeutic uses
INVENTOR(S): Mullally, James E.; Moos, Philip; Fitzpatrick, Frank A.
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004009023	A2	20040129	WO 2003-US22576	20030718
WO 2004009023	A3	20040617		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,

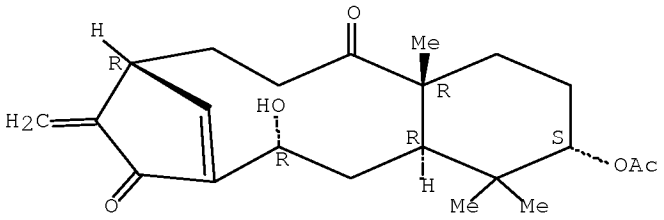
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2492523	A1	20040129	CA 2003-2492523	20030718
AU 2003249320	A1	20040209	AU 2003-249320	20030718
EP 1542682	A2	20050622	EP 2003-765765	20030718
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 20060106099	A1	20060518	US 2005-521570	20051107
PRIORITY APPLN. INFO.:			US 2002-396584P	P 20020718
			WO 2003-US22576	W 20030718

AB A novel class of inhibitors of ubiquitin isopeptidases is disclosed that cause tumor cell death via mol. mechanisms independent of p53. Specifically, compds. containing an α,β-unsatd. ketone with a sterically accessible electrophilic β-carbon and related compds. are identified herein. The α-carbon of at least one α,β-unsatd. ketone moiety bears an electron withdrawing substituent which is selected from the group consisting of fluorine, chlorine, bromine, iodine, nitro, nitrilo and carboxy. The said carboxy group is an acid, ester of amide group. The said α,β-unsatd. ketone comprises a conjugated cyclopentene moiety. Pharmaceutical compns. comprising the inhibitor compds. and methods of using the compds. for treating a variety of disease , such as tumor, inflammation, autoimmune disease, restenosis and dry eye, are disclosed.

IT 73211-11-7, Shikoccin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NSC 302979; α,β-unsatd. ketone as inhibitors of ubiquitin isopeptidases that induce p53-independent cell death and their therapeutic uses)
RN 73211-11-7 HCAPLUS
CN 10,7-Metheno-7H-benzocycloundecene-8,13-dione, 3-(acetyloxy)-1,2,3,4,4a,5,6,9,10,11,12,13a-dodecahydro-6-hydroxy-4,4,13a-trimethyl-9-methylene-, (3S,4aR,6R,10R,13aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 9037-42-7, DNA methyltransferase 140879-24-9, Proteasome 142805-56-9, DNA topoisomerase II 143180-75-0, DNA topoisomerase I
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; α,β-unsatd. ketone as inhibitors of ubiquitin isopeptidases that induce p53-independent cell death and their therapeutic uses)
RN 9037-42-7 HCAPLUS
CN Methyltransferase, deoxyribonucleate (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 140879-24-9 HCAPLUS
CN Proteinase, multicatalytic (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

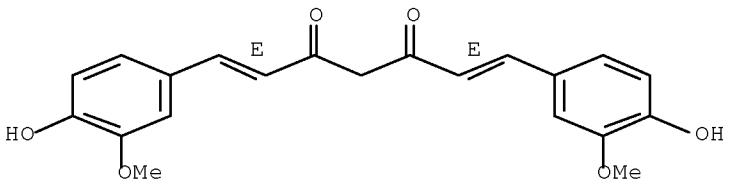
RN 142805-56-9 HCAPLUS
CN Isomerase, deoxyribonucleate topo-, II (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 143180-75-0 HCAPLUS
CN Isomerase, deoxyribonucleate topo-, I (CA INDEX NAME)

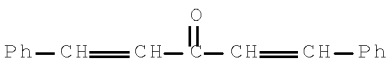
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT 86480-67-3, Ubiquitin isopeptidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α,β-unsatd. ketone as inhibitors of ubiquitin isopeptidases that induce p53-independent cell death and their therapeutic uses)
RN 86480-67-3 HCAPLUS
CN Hydrolase, ubiquitin thiolester (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT 458-37-7, Curcumin 538-58-9, Dibenzylideneacetone
1029-96-5, 2,6-Diphenyl-4H-thiopyran-4-one 5956-04-7,
NSC 156236 13345-51-2, PGB1 33069-62-4, Taxol
33419-42-0, Etoposide 79655-73-5 87893-54-7,
Δ12-PGJ2 96055-64-0 96055-65-1
96055-66-2 96055-68-4 133407-86-0, MG115
160791-07-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α,β-unsatd. ketone as inhibitors of ubiquitin isopeptidases that induce p53-independent cell death and their therapeutic uses)
RN 458-37-7 HCAPLUS
CN 1,6-Heptadiene-3,5-dione, 1,7-bis(4-hydroxy-3-methoxyphenyl)-, (1E,6E)- (CA INDEX NAME)

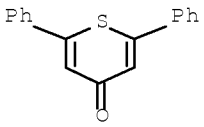
Double bond geometry as shown.



RN 538-58-9 HCAPLUS
CN 1,4-Pentadien-3-one, 1,5-diphenyl- (CA INDEX NAME)

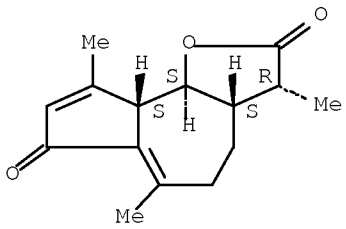


RN 1029-96-5 HCAPLUS
CN 4H-Thiopyran-4-one, 2,6-diphenyl- (CA INDEX NAME)



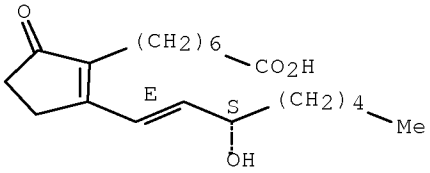
RN 5956-04-7 HCAPLUS
CN Azuleno[4,5-b]furan-2,7-dione, 3,3a,4,5,9a,9b-hexahydro-3,6,9-trimethyl-, (3R,3aS,9aS,9bS)- (CA INDEX NAME)

Absolute stereochemistry.



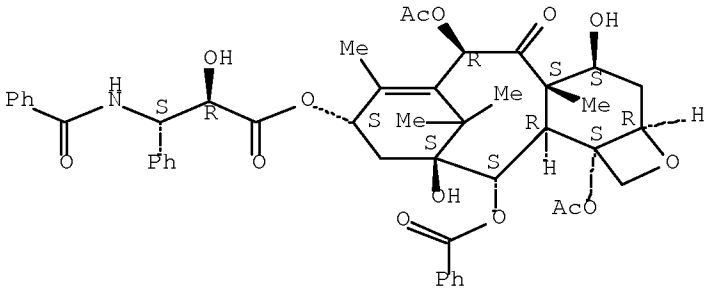
RN 13345-51-2 HCAPLUS
CN Prosta-8(12),13-dien-1-oic acid, 15-hydroxy-9-oxo-, (13E,15S)- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



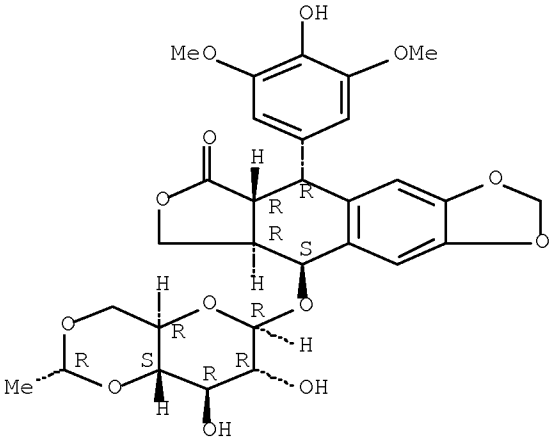
RN 33069-62-4 HCAPLUS
CN Benzenepropanoic acid, β-(benzoylamino)-α-hydroxy-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, (αR,βS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

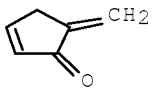


RN 33419-42-0 HCAPLUS
CN Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one, 9-[[4,6-O-(1R)-ethylidene-β-D-glucopyranosyl]oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-, (5R,5aR,8aR,9S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

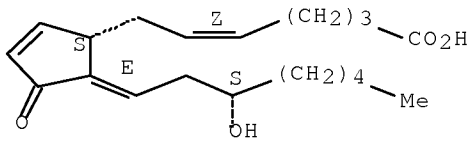


RN 79655-73-5 HCAPLUS
CN 2-Cyclopenten-1-one, 5-methylene- (CA INDEX NAME)



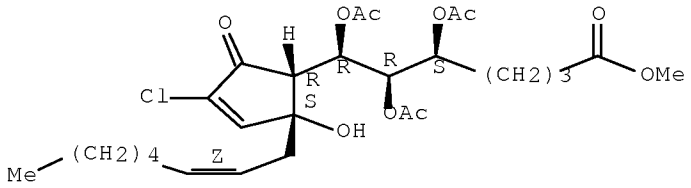
RN 87893-54-7 HCAPLUS
CN Prosta-5,9,12-trien-1-oic acid, 15-hydroxy-11-oxo-, (5Z,12E,15S)- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



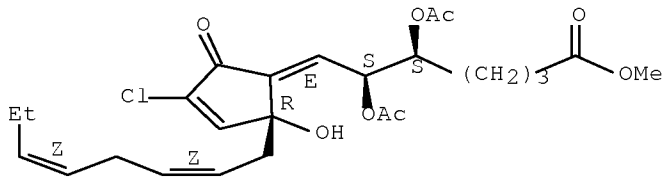
RN 96055-64-0 HCAPLUS
CN Prosta-10,14-dien-1-oic acid, 5,6,7-tris(acetyloxy)-10-chloro-12-hydroxy-9-oxo-, methyl ester, (5S,6R,7R,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



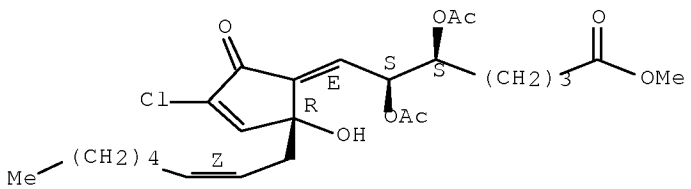
RN 96055-65-1 HCAPLUS
CN Prosta-7,10,14,17-tetraen-1-oic acid, 5,6-bis(acetyloxy)-10-chloro-12-hydroxy-9-oxo-, methyl ester, (5S,6S,7E,14Z,17Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 96055-66-2 HCAPLUS
CN Prosta-7,10,14-trien-1-oic acid, 5,6-bis(acetyloxy)-10-chloro-12-hydroxy-9-oxo-, methyl ester, (5S,6S,7E,14Z)- (9CI) (CA INDEX NAME)

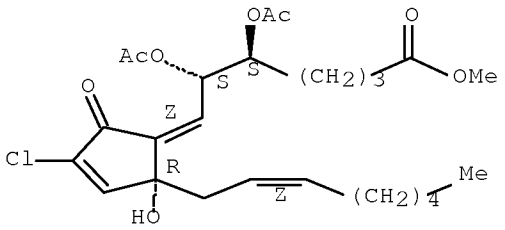
Absolute stereochemistry.
Double bond geometry as shown.



RN 96055-68-4 HCAPLUS
CN Prosta-7,10,14-trien-1-oic acid, 5,6-bis(acetyloxy)-10-chloro-12-hydroxy-9-

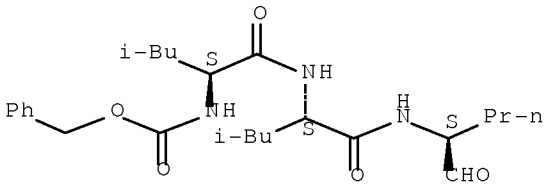
oxo-, methyl ester, (5S,6S,7Z,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



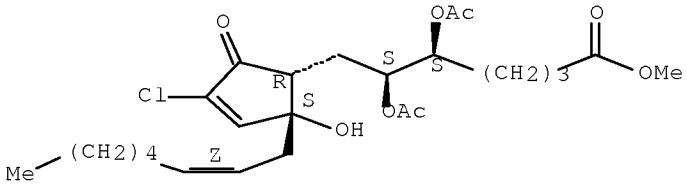
RN 133407-86-0 HCAPLUS
CN L-Leucinamide, N-[(phenylmethoxy)carbonyl]-L-leucyl-N-[(1S)-1-formylbutyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 160791-07-1 HCAPLUS
CN Prosta-10,14-dien-1-oic acid, 5,6-bis(acetyloxy)-10-chloro-12-hydroxy-9-oxo-, methyl ester, (5S,6S,14Z)- (9CI) (CA INDEX NAME)

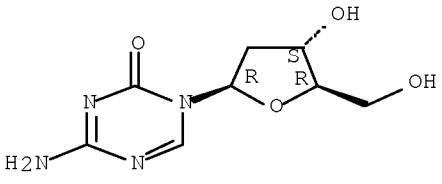
Absolute stereochemistry.
Double bond geometry as shown.



IT 2353-33-5, Decitabine 7689-03-4D, Camptothecin, analog 71503-81-6, Shikodomedin 83159-26-6, O-Methyl shikoccin 83159-28-8, O-Methylepoxyskikoccin 89354-63-2, Rabdolatifolin 123941-77-5, Rabdoumbrosanin 155545-33-8, RabdoShikoccin A 155545-34-9, RabdoShikoccin B
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α,β-unsatd. ketone as inhibitors of ubiquitin isopeptidases that induce p53-independent cell death and their therapeutic uses)
RN 2353-33-5 HCAPLUS
CN 1,3,5-Triazin-2(1H)-one, 4-amino-1-(2-deoxy-β-D-erythro-

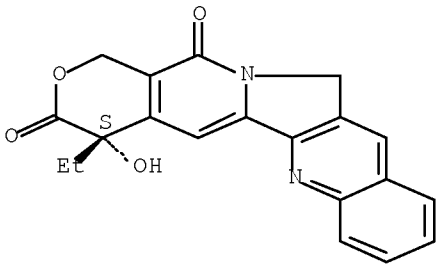
pentofuranosyl)- (CA INDEX NAME)

Absolute stereochemistry.

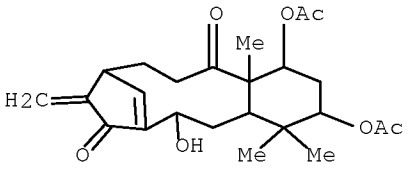


RN 7689-03-4 HCAPLUS
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-, (4S)- (CA INDEX NAME)

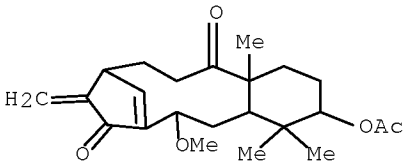
Absolute stereochemistry. Rotation (+).



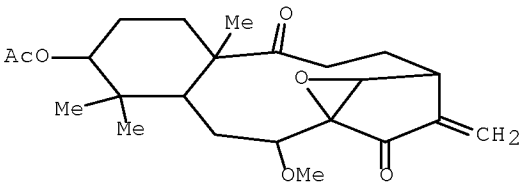
RN 71503-81-6 HCAPLUS
CN 10,7-Metheno-7H-benzocycloundecene-8,13-dione, 1,3-bis(acetyloxy)-1,2,3,4,4a,5,6,9,10,11,12,13a-dodecahydro-6-hydroxy-4,4,13a-trimethyl-9-methylene-, (1S,3S,4aR,6R,10R,13aS)- (9CI) (CA INDEX NAME)



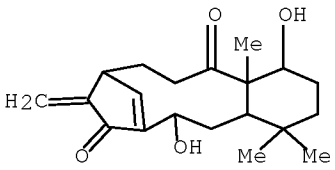
RN 83159-26-6 HCAPLUS
CN 10,7-Metheno-7H-benzocycloundecene-8,13-dione, 3-(acetyloxy)-1,2,3,4,4a,5,6,9,10,11,12,13a-dodecahydro-6-methoxy-4,4,13a-trimethyl-9-methylene-, (3S,4aR,6R,10R,13aR)- (9CI) (CA INDEX NAME)



RN 83159-28-8 HCAPLUS
CN 5H-2,11a-Ethanobenzo[5,6]cyclodec[1,2-b]oxirene-5,12-dione, 8-(acetyloxy)dodecahydro-11-methoxy-5a,9,9-trimethyl-13-methylene-, (1aR,2S,5aR,8S,9aR,11R,11aR)- (9CI) (CA INDEX NAME)

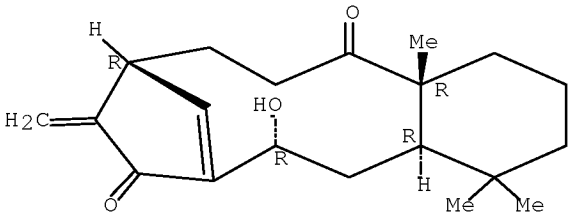


RN 89354-63-2 HCAPLUS
CN 10,7-Metheno-7H-benzocycloundecene-8,13-dione, 1,2,3,4,4a,5,6,9,10,11,12,13a-dodecahydro-1,6-dihydroxy-4,4,13a-trimethyl-9-methylene-, (1S,4aR,6R,10R,13aS)- (9CI) (CA INDEX NAME)



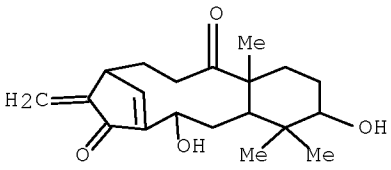
RN 123941-77-5 HCAPLUS
CN 10,7-Metheno-7H-benzocycloundecene-8,13-dione, 1,2,3,4,4a,5,6,9,10,11,12,13a-dodecahydro-6-hydroxy-4,4,13a-trimethyl-9-methylene-, (4aR,6R,10R,13aR)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

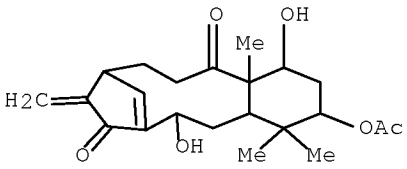


RN 155545-33-8 HCAPLUS
CN 10,7-Metheno-7H-benzocycloundecene-8,13-dione,

1,2,3,4,4a,5,6,9,10,11,12,13a-dodecahydro-3,6-dihydroxy-4,4,13a-trimethyl-9-methylene-, (3R,4aR,6R,10R,13aR)- (9CI) (CA INDEX NAME)



RN 155545-34-9 HCAPLUS
CN 10,7-Metheno-7H-benzocycloundecene-8,13-dione, 3-(acetyloxy)-1,2,3,4,4a,5,6,9,10,11,12,13a-dodecahydro-1,6-dihydroxy-4,4,13a-trimethyl-9-methylene-, (1S,3S,4aR,6R,10R,13aS)- (9CI) (CA INDEX NAME)



L4 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:976359 HCAPLUS Full-text
DOCUMENT NUMBER: 140:231410
TITLE: Discovery of novel effectors of the proteasome pathway: cyclopentenones as inhibitors of ubiquitin isopeptidase activity
AUTHOR(S): Mullally, James Edward
CORPORATE SOURCE: Univ. of Utah, Salt Lake City, UT, USA
SOURCE: (2003) 104 pp. Avail.: UMI, Order No. DA3077655
From: Diss. Abstr. Int., B 2003, 64(1), 222
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable
IT 86480-67-3, Ubiquitin isopeptidase
140879-24-9, Proteasome
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cyclopentenones as inhibitors of ubiquitin isopeptidase activity)
RN 86480-67-3 HCAPLUS
CN Hydrolase, ubiquitin thiolester (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 140879-24-9 HCAPLUS
CN Proteinase, multicatalytic (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:577816 HCAPLUS Full-text
DOCUMENT NUMBER: 138:147170

TITLE: Pharmacophore model for novel inhibitors of ubiquitin isopeptidases that induce p53-independent cell death
AUTHOR(S): Mullally, J. E.; Fitzpatrick, F. A.
CORPORATE SOURCE: Huntsman Cancer Institute, Department of Medicinal Chemistry, University of Utah, Salt Lake City, UT, USA
SOURCE: Molecular Pharmacology (2002), 62(2), 351-358
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The tumor suppressor p53 is mutated in more than 50% of all cancers. Importantly, most clin. useful antineoplastic agents are less potent and efficacious in the context of mutant p53. This situation has prompted a search for agents that cause tumor cell death via mol. mechanisms independent of p53. Our recent investigations with electrophilic prostaglandins enabled us to devise a pharmacophore and mechanism of action hypothesis relevant to this problem: a cross-conjugated α,β-unsatd. dienone with two sterically accessible electrophilic β-carbons is a mol. determinant that confers activity among this class of ubiquitin isopeptidases inhibitors, and that inhibitors of ubiquitin isopeptidases cause cell death in vitro independently of p53. Here, we report the use of the National Cancer Institute's Developmental Therapeutics Database to identify compds. to test this hypothesis. Shikoccin (a diterpene), dibenzylideneacetone, and curcumin fit the pharmacophore hypothesis, inhibit cellular isopeptidases, and cause cell death independently of p53 in isogenic pairs of RKO and HCT 116 cells with differential p53 status. The sesquiterpene achillin and 2,6-diphenyl-4H-thiopyran-4-one, which have cross-conjugated dienones with sterically hindered electrophilic β-carbons, do not inhibit isopeptidases or cause significant cell death. Furthermore, we show that a catalytic-site proteasome inhibitor causes cell death independently of p53. Combined, these data verify the p53-independence of cell death caused by inhibitors of the proteasome pathway and support the proposition that the ubiquitin-dependent proteasome pathway may contain mol. targets suitable for antineoplastic drug discovery.

IT 140879-24-9, Proteasome
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(catalytic-site, inhibitor; pharmacophore model for novel inhibitors of ubiquitin isopeptidases that induce p53-independent cell death)
RN 140879-24-9 HCAPLUS
CN Proteinase, multicatalytic (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

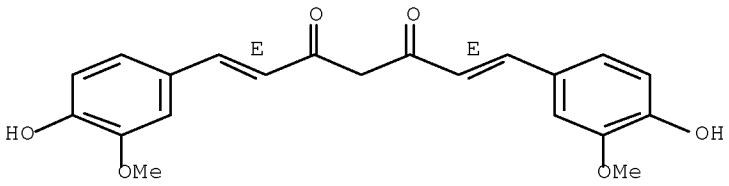
IT 86480-67-3, Ubiquitin isopeptidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacophore model for novel inhibitors of ubiquitin isopeptidases that induce p53-independent cell death)
RN 86480-67-3 HCAPLUS
CN Hydrolase, ubiquitin thiolester (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

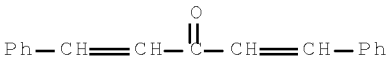
IT 458-37-7, Curcumin 538-58-9, Dibenzylideneacetone
1029-96-5, 2,6-Diphenyl-4H thiopyran-4-one 5956-04-7,
Achillin 73211-11-7, Shikoccin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacophore model for novel inhibitors of ubiquitin isopeptidases that induce p53-independent cell death)

RN 458-37-7 HCAPLUS
CN 1,6-Heptadiene-3,5-dione, 1,7-bis(4-hydroxy-3-methoxyphenyl)-, (1E,6E)-
(CA INDEX NAME)

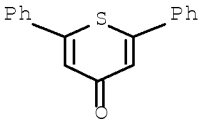
Double bond geometry as shown.



RN 538-58-9 HCAPLUS
CN 1,4-Pentadien-3-one, 1,5-diphenyl- (CA INDEX NAME)

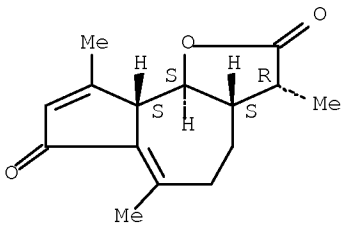


RN 1029-96-5 HCAPLUS
CN 4H-Thiopyran-4-one, 2,6-diphenyl- (CA INDEX NAME)



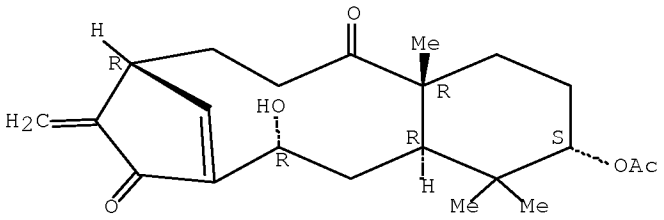
RN 5956-04-7 HCAPLUS
CN Azuleno[4,5-b]furan-2,7-dione, 3,3a,4,5,9a,9b-hexahydro-3,6,9-trimethyl-,
(3R,3aS,9aS,9bS)- (CA INDEX NAME)

Absolute stereochemistry.



RN 73211-11-7 HCAPLUS
CN 10,7-Metheno-7H-benzocycloundecene-8,13-dione, 3-(acetyloxy)-
1,2,3,4,4a,5,6,9,10,11,12,13a-dodecahydro-6-hydroxy-4,4,13a-trimethyl-9-
methylene-, (3S,4aR,6R,10R,13aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:613266 HCAPLUS Full-text
DOCUMENT NUMBER: 135:299034
TITLE: Cyclopentenone prostaglandins of the J series inhibit the ubiquitin isopeptidase activity of the proteasome pathway
AUTHOR(S): Mullally, James E.; Moos, Philip J.; Edes, Kornelia; Fitzpatrick, Frank A.
CORPORATE SOURCE: Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, 84108, USA
SOURCE: Journal of Biological Chemistry (2001), 276(32), 30366-30373
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Electrophilic eicosanoids of the J series, with their distinctive cross-conjugated α,β-unsatd. ketone, inactivate genetically wild type tumor suppressor p53 in a manner analogous to prostaglandins of the A series. Like the prostaglandins of the A series, prostaglandins of the J series have a structural determinant (endocyclic cyclopentenone) that confers the ability to impair the conformation, the phosphorylation, and the transcriptional activity of the p53 tumor suppressor with equivalent potency and efficacy. However, J series prostaglandins have a unique structural determinant (exocyclic α,β-unsatd. ketone) that confers unique efficacy as an apoptotic agonist. In seeking to understand how J series prostaglandins cause apoptosis despite their inactivation of p53, we discovered that they inhibit the ubiquitin isopeptidase activity of the proteasome pathway. In this regard, J series prostaglandins were more efficacious inhibitors than representative members of the A, B, or E series prostaglandins. Disruption of the proteasome pathway with proteasome inhibitors can cause apoptosis independently of p53. Therefore, this finding helps reconcile the p53 transcriptional independence of apoptosis caused by Δ12-prostaglandin J2. This discovery represents a novel mechanism for proteasome pathway inhibition in intact cells. Furthermore, it identifies isopeptidases as novel targets for the development of antineoplastic agents.

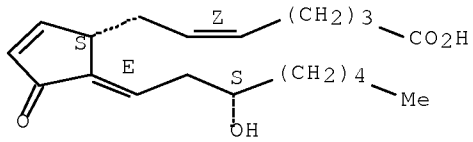
IT 86480-67-3, Ubiquitin isopeptidase
140879-24-9, Proteasome
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclopentenone prostaglandins of the J series inhibit the ubiquitin isopeptidase activity of the proteasome pathway)

RN 86480-67-3 HCAPLUS
CN Hydrolase, ubiquitin thiolester (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 140879-24-9 HCAPLUS
CN Proteinase, multicatalytic (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT 87893-54-7, Δ12-Prostaglandin J2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cyclopentenone prostaglandins of the J series inhibit the ubiquitin isopeptidase activity of the proteasome pathway)
RN 87893-54-7 HCAPLUS
CN Prosta-5,9,12-trien-1-oic acid, 15-hydroxy-11-oxo-, (5Z,12E,15S)- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(Please note, all retrieved items are later than earliest priority date.)

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L5            1 SEA FILE=REGISTRY ABB=ON  96055-64-0/RN
L8            7 SEA FILE=HCAPLUS ABB=ON  L5
L9            1 SEA FILE=REGISTRY ABB=ON  "UBIQUITIN ISOPEPTIDASE"/CN
L10           2 SEA FILE=HCAPLUS ABB=ON  L8 AND (L9 OR ?UBIQUITIN?(W)?ISOPEPTID
                ASE?)
L11           1 SEA FILE=USPATFULL ABB=ON  L8 AND (L9 OR ?UBIQUITIN?(W)?ISOPEPT
                IDASE?)
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L13           0 SEA L12 AND (PRD<20020718 OR PD<20020718)


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L12  ANSWER 1 OF 3  USPATFULL on STN
ACCESSION NUMBER:       2006:125364  USPATFULL  Full-text
TITLE:                  Novel inhibitors of ubiquitin
                        isopeptidases
INVENTOR(S):            Mullally, James E, UNITED STATES

                             NUMBER       KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 2006106099      A1   20060518
APPLICATION INFO.:      US 2003-521570     A1   20030718  (10)
                        WO 2003-US22576         20030718
                                                20051107  PCT 371 date

                               NUMBER         DATE
                        ------------------ --------
PRIORITY INFORMATION:   US 2002-60395584   20020718
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
LEGAL REPRESENTATIVE:   HELLER EHRMAN WHITE & MCAULIFFE LLP, 1717 RHODE ISLAND
                        AVE, NW, WASHINGTON, DC, 20036-3001, US
NUMBER OF CLAIMS:       38
EXEMPLARY CLAIM:        1
NUMBER OF DRAWINGS:     7 Drawing Page(s)
LINE COUNT:             1670
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      A novel class of inhibitors of ubiquitin isopeptidases is disclosed that
        cause tumor cell death via molecular mechanisms independent of p53.
        Specifically, compounds containing an a,β-unsaturated ketone with a
        sterically accessible electrophilic β-carbon and related compounds are
        identified herein. Pharmaceutical compositions comprising the inhibitor
        compounds and methods of using the compounds for treating a variety of
        disease states are disclosed.


CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT  86480-67-3, Ubiquitin isopeptidase
        (α,β-unsatd. ketone as inhibitors of ubiquitin isopeptidases
        that induce p53-independent cell death and their therapeutic uses)
RN   86480-67-3  USPATFULL
CN   Hydrolase, ubiquitin thiolester  (CA INDEX NAME)
```

STRUCTURE DIAGRAM IS NOT AVAILABLE

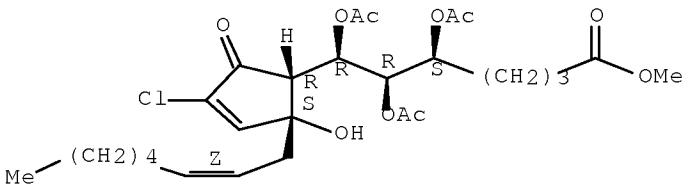
IT 96055-64-0

(α,β-unsatd. ketone as inhibitors of ubiquitin isopeptidases that induce p53-independent cell death and their therapeutic uses)

RN 96055-64-0 USPATFULL

CN Prosta-10,14-dien-1-oic acid, 5,6,7-tris(acetyloxy)-10-chloro-12-hydroxy-9-oxo-, methyl ester, (5S,6R,7R,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L12 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:80455 HCAPLUS Full-text

DOCUMENT NUMBER: 140:139470

TITLE: α,β-unsaturated ketone as inhibitors of ubiquitin isopeptidases that induce p53-independent cell death and their therapeutic uses

INVENTOR(S): Mullally, James E.; Moos, Philip; Fitzpatrick, Frank A.

PATENT ASSIGNEE(S): University of Utah Research Foundation, USA

SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004009023	A2	20040129	WO 2003-US22576	20030718
WO 2004009023	A3	20040617		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2492523	A1	20040129	CA 2003-2492523	20030718
AU 2003249320	A1	20040209	AU 2003-249320	20030718
EP 1542682	A2	20050622	EP 2003-765765	20030718
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US 20060106099	A1	20060518	US 2005-521570	20051107

PRIORITY APPLN. INFO.:

US 2002-396584P	P	20020718
WO 2003-US22576	W	20030718

AB A novel class of inhibitors of ubiquitin isopeptidases is disclosed that cause tumor cell death via mol. mechanisms independent of p53. Specifically, compds. containing an α,β-unsatd. ketone with a sterically accessible electrophilic β-carbon and related compds. are identified herein. The α-carbon of at least one α,β-unsatd. ketone moiety bears an electron withdrawing substituent which is selected from the group consisting of fluorine, chlorine, bromine, iodine, nitro, nitrilo and carboxy. The said carboxy group is an acid, ester of amide group. The said α,β-unsatd. ketone comprises a conjugated cyclopentene moiety. Pharmaceutical compns. comprising the inhibitor compds. and methods of using the compds. for treating a variety of disease , such as tumor, inflammation, autoimmune disease, restenosis and dry eye, are disclosed.

IT 86480-67-3, Ubiquitin isopeptidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α,β-unsatd. ketone as inhibitors of ubiquitin isopeptidases that induce p53-independent cell death and their therapeutic uses)

RN 86480-67-3 HCAPLUS

CN Hydrolase, ubiquitin thiolester (CA INDEX NAME)

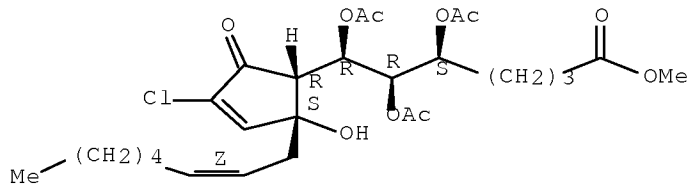
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 96055-64-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α,β-unsatd. ketone as inhibitors of ubiquitin isopeptidases that induce p53-independent cell death and their therapeutic uses)

RN 96055-64-0 HCAPLUS

CN Prosta-10,14-dien-1-oic acid, 5,6,7-tris(acetyloxy)-10-chloro-12-hydroxy-9-oxo-, methyl ester, (5S,6R,7R,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L12 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:195003 HCAPLUS Full-text

DOCUMENT NUMBER: 140:385609

TITLE: Punaglandins, chlorinated prostaglandins, function as potent michael receptors to inhibit ubiquitin isopeptidase activity

AUTHOR(S): Verbitski, Sheryl M.; Mullally, James E.; Fitzpatrick, Frank A.; Ireland, Chris M.

CORPORATE SOURCE: Department of Medicinal Chemistry, University of Utah, Salt Lake City, UT, 84112, USA

SOURCE: Journal of Medicinal Chemistry (2004), 47(8), 2062-2070
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cyclopentenone prostaglandins exhibit unique antineoplastic activity and are potent growth inhibitors in a variety of cultured cells. Recently the dienone prostaglandin, Δ12-PGJ2, was shown to preferentially inhibit ubiquitin isopeptidase activity of the proteasome pathway. It is theorized that isopeptidase inhibition and general cytotoxicity of prostaglandins depend on olefin-ketone conjugation, electrophilic accessibility, and the nucleophilic reactivity of the endocyclic β-carbon. Δ12-PGJ2, which contains a cross-conjugated α,β-unsatd. ketone, was a potent inhibitor of isopeptidase activity, whereas PGA1 and PGA2 with simple α,β-unsatd. pentenones were significantly less potent and PGB1 with a sterically hindered α,β-unsatd. ketone was inactive. To further investigate the proposed mechanism, punaglandins, which are highly functional cyclopentadienone and cyclopentenone prostaglandins chlorinated at the endocyclic α-carbon position, were isolated from the soft coral Telesto riisei. They were then assayed for inhibition of ubiquitin isopeptidase activity and antineoplastic effects. The punaglandins were shown to inhibit isopeptidase activity and exhibit antiproliferative effects more potently than A and J series prostaglandins. Also, the cross-conjugated dienone punaglandin was more potent than the simple enone punaglandin. The ubiquitin-proteasome pathway is a vital component of cellular metabolism and may be a suitable target for antineoplastic agents. These newly characterized proteasome inhibitors may represent a new chemical class of cancer therapeutics.

IT 86480-67-3, Ubiquitin isopeptidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(punaglandins function as potent michael receptors To inhibit ubiquitin isopeptidase activity)

RN 86480-67-3 HCAPLUS

CN Hydrolase, ubiquitin thiolester (CA INDEX NAME)

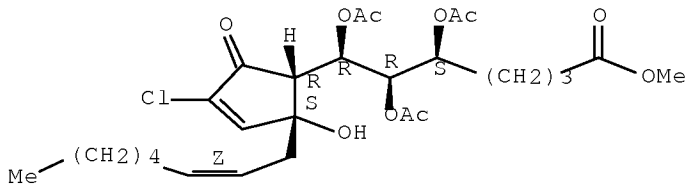
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 96055-64-0P, Punaglandin 2
RL: PAC (Pharmacological activity); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(punaglandins function as potent michael receptors To inhibit ubiquitin isopeptidase activity)

RN 96055-64-0 HCAPLUS

CN Prosta-10,14-dien-1-oic acid, 5,6,7-tris(acetyloxy)-10-chloro-12-hydroxy-9-oxo-, methyl ester, (5S,6R,7R,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SEARCH HISTORY

=> d his ful

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     (FILE 'HOME' ENTERED AT 14:58:22 ON 28 MAY 2008)

     FILE 'HCAPLUS' ENTERED AT 14:58:35 ON 28 MAY 2008
                E MULLALLY JAMES E/AU
L1           15 SEA ABB=ON  ("MULLALLY J E"/AU OR "MULLALLY JAMES"/AU OR
                "MULLALLY JAMES E"/AU OR "MULLALLY JAMES EDWARD"/AU)
L2            5 SEA ABB=ON  L1 AND ?UBIQUITIN?(W)?ISOPEPTIDASE?
                SELECT RN L2 1-5

     FILE 'REGISTRY' ENTERED AT 15:00:22 ON 28 MAY 2008
L3           30 SEA ABB=ON  (86480-67-3/BI OR 140879-24-9/BI OR 1029-96-5/BI
                OR 160791-07-1/BI OR 458-37-7/BI OR 538-58-9/BI OR 5956-04-7/BI
                 OR 73211-11-7/BI OR 87893-54-7/BI OR 96055-64-0/BI OR
                96055-65-1/BI OR 96055-66-2/BI OR 96055-68-4/BI OR 123941-77-5/
                BI OR 133407-86-0/BI OR 13345-51-2/BI OR 142805-56-9/BI OR
                143180-75-0/BI OR 155545-33-8/BI OR 155545-34-9/BI OR 2353-33-5
                /BI OR 33069-62-4/BI OR 33419-42-0/BI OR 71503-81-6/BI OR
                7689-03-4/BI OR 79655-73-5/BI OR 83159-26-6/BI OR 83159-28-8/BI
                 OR 89354-63-2/BI OR 9037-42-7/BI)

     FILE 'HCAPLUS' ENTERED AT 15:00:27 ON 28 MAY 2008
L4            5 SEA ABB=ON  L2 AND L3
                D IBIB ABS HITSTR L4 1-5

     FILE 'REGISTRY' ENTERED AT 15:05:12 ON 28 MAY 2008
L5            1 SEA ABB=ON  96055-64-0/RN
L6              STRUCTURE  96055-64-0
L7            0 SEA SSS SAM L6

     FILE 'HCAPLUS' ENTERED AT 15:06:24 ON 28 MAY 2008
L8            7 SEA ABB=ON  L5

     FILE 'REGISTRY' ENTERED AT 15:06:36 ON 28 MAY 2008
                E UBIQUITIN ISOPEPTIDASE/CN
L9            1 SEA ABB=ON  "UBIQUITIN ISOPEPTIDASE"/CN

     FILE 'HCAPLUS' ENTERED AT 15:06:50 ON 28 MAY 2008
L10           2 SEA ABB=ON  L8 AND (L9 OR ?UBIQUITIN?(W)?ISOPEPTIDASE?)

     FILE 'USPATFULL' ENTERED AT 15:07:35 ON 28 MAY 2008
L11           1 SEA ABB=ON  L8 AND (L9 OR ?UBIQUITIN?(W)?ISOPEPTIDASE?)

     FILE 'HCAPLUS, USPATFULL' ENTERED AT 15:07:45 ON 28 MAY 2008
L12           3 DUP REMOV L10 L11 (0 DUPLICATES REMOVED)
L13           0 SEA ABB=ON  L12 AND (PRD<20020718 OR PD<20020718)

     FILE 'MEDLINE, BIOSIS, EMBASE, DRUGU' ENTERED AT 15:08:14 ON 28 MAY 2008
L14           0 SEA ABB=ON  L10

     FILE HOME

     FILE HCAPLUS

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 MAY 2008 HIGHEST RN 1023132-78-6
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FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 May 2008 (20080527/PD)
FILE LAST UPDATED: 27 May 2008 (20080527/ED)
HIGHEST GRANTED PATENT NUMBER: US7380282
HIGHEST APPLICATION PUBLICATION NUMBER: US2008120751
CA INDEXING IS CURRENT THROUGH 27 May 2008 (20080527/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 May 2008 (20080527/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2008
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Apr 2008

FILE MEDLINE
FILE LAST UPDATED: 27 May 2008 (20080527/UP). FILE COVERS 1949 TO DATE.

MEDLINE has been updated with the National Library of Medicine's revised 2008 MeSH terms. See HELP RLOAD for details.

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FILE BIOSIS

FILE COVERS 1926 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1926 TO DATE.

RECORDS LAST ADDED: 21 May 2008 (20080521/ED)

BIOSIS has been augmented with 1.8 million archival records from 1926 through 1968. These records have been re-indexed to match current BIOSIS indexing.

FILE EMBASE
FILE COVERS 1974 TO 28 May 2008 (20080528/ED)

EMBASE was reloaded on March 30, 2008.

EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

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FILE LAST UPDATED: 23 MAY 2008 <20080523/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
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